Chapter I

Carbon hetero bond formation reactions and a brief overview

I.A. Introduction to carbon-hetero bond

The major function of many organic compounds is often derived from the presence of heteroatoms in their structure. Presence of atoms like nitrogen, oxygen, phosphorous, sulfur etc. often amplifies the applicability of organic compounds for biological, agrochemical as well as vast field of chemistry. For instance, most of the major pharmaceuticals often consist of C-O, C-N or C-S bond and almost all natural products also have the same. Another advantage of these C-Heterocyclic ring formation in organic compounds is that, they can bind with metals or metal ions by complex formation and form stable compounds which have vast array of application in organic and even inorganic field. An easy example of such is chlorophyll and hemoglobin which are stabilized by the presence of nitrogen ligand. These compounds are also treated as a strong precursor for synthesis of many biological product which occur in nature like glycosides, amino acids etc. The applicability of these compound can be seen in many available drugs in current market.

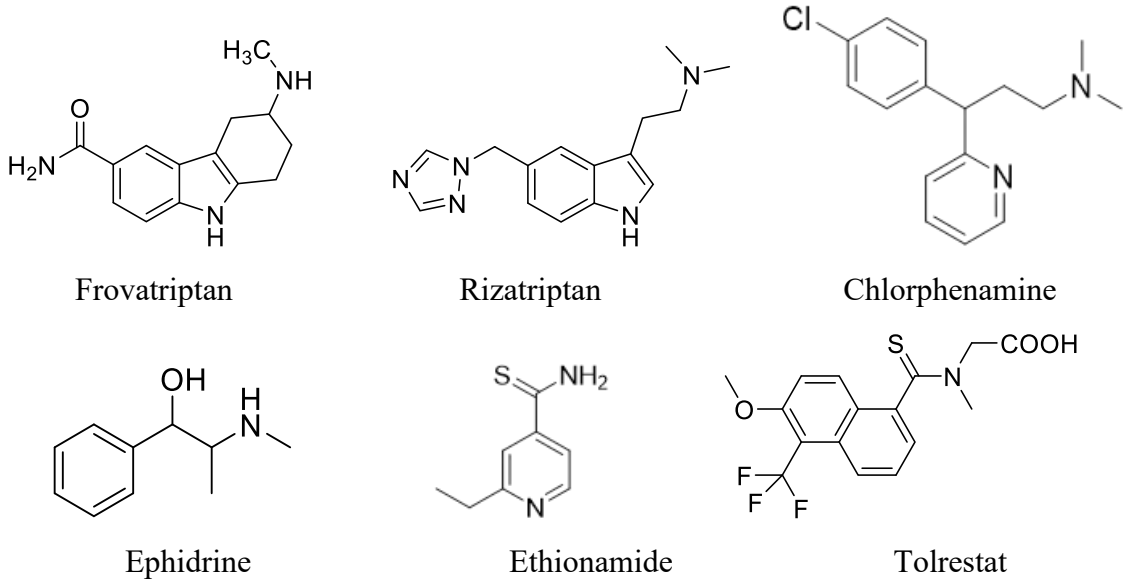


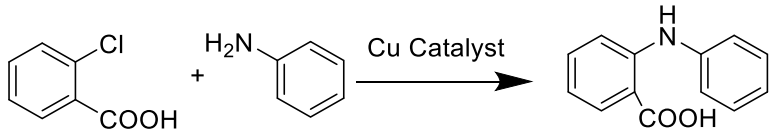
Figure I.1. Biologically active C-Hetero bonded compounds.

Various methodologies have been discovered for the synthesis of C-hetero compound synthesis reactions. Here we represent a brief review of the prominent work on formation of various C-hetero compound formation reactions.

I.A.1. C-N bond formation reaction

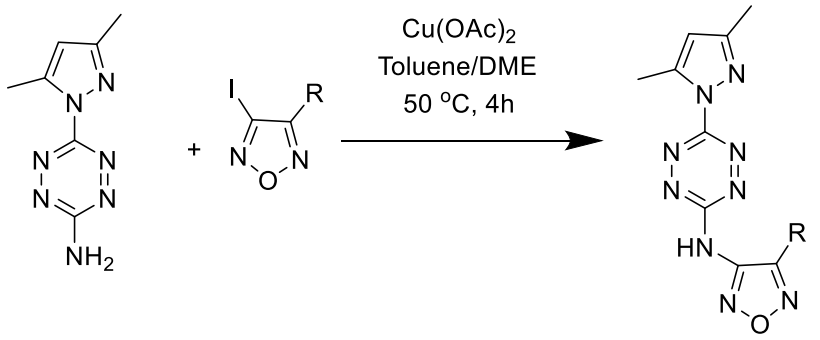
Compounds having C-N bond like, amines, enamines. Isocyanides, azides, imines, amides, lactums, carbamates, imides, thioamides, thioureas, amidines, sulfonamides, cyanamides, guanidines, urea and its derivatives, hydrazones, isocyanatesaziridines, nitro compounds and their derivatives etc. are extremely important today in organic and overall chemical fields. In recent years notable advantages have been found where other transition metals and even metal-

free conditions are also used. Metal catalyzed synthesis of C-N coupling reaction was used by Ullmann (Scheme I.1) and Goldberg in 1903[1,2]. They have used Cu as catalyst for C-N bond formation.



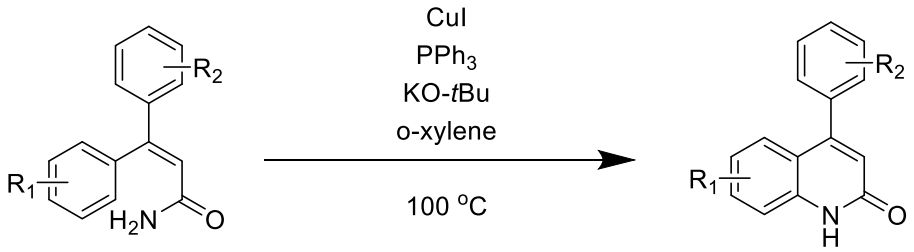
Scheme I.1. Synthesis of diphenyl amine by Cu catalyst.

In present time M. Yu. Antipin *et al.* developed a robust method for the coupling of a variety of furazanyl iodides with 1,2,4,5-tetrazines[3] (Scheme I.2) where they have employed $Cu(OAc)_2$ as catalyst at 50°C. Here electron-deficient nitrogen-rich heterocyclic iodides were coupled with electron-deficient nitrogen-rich heterocyclic amines to yield tetrazine.



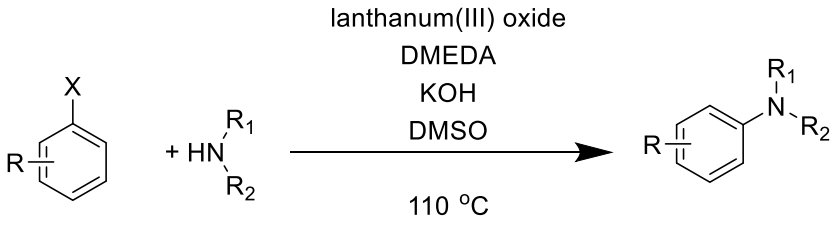
Scheme I.2. Coupling reaction of furazanyl iodides with 5-tetrazinylamines by $Cu(OAc)_2$.

A. Goggiamani *et al.* developed another Cu catalyzed protocol for construction of 2-quinolines based on an intramolecular C-N bond forming process[4] (Scheme I.3) . They produced good yield by using CuI and PPh_3 in presence of KO-*t*Bu at 100 °C in *o*-xylene.



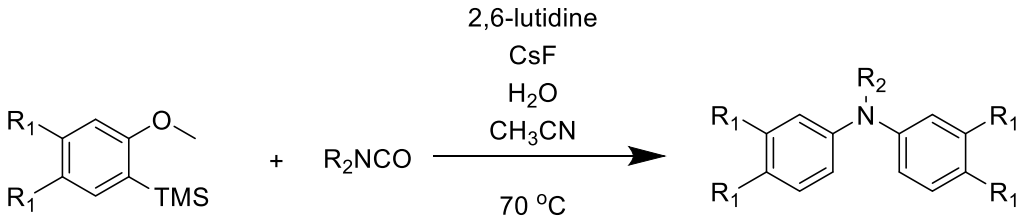
Scheme I.3. Synthesis of 2-quinolones by CuI in PPh_3 and KO-*t*Bu.

Other transition metals than Cu are also employed successfully for C-N bond formation reaction. Recently aryl halides are coupled with aromatic and heteroaromatic amines by Y. V. D. Nageswar *et al.* using lanthanum(III) oxide, DMEDA and KOH as base in DMSO[5] (Scheme I.4). It has been noticed that electron donating and withdrawing groups on iodobenzene and nitrogen nucleophile have no significant effect on the product yield of the C–N cross-coupled product.



Scheme I.4. Synthesis of *N*-arylated derivatives by lanthanum(III) oxide.

Nowadays, metal-free approach for a particular bond formation is of huge interest. Following that trend C-N bond formation has also been successfully done in metal-free condition. Coupling of isocyanates and benzynes have been discovered by J.C. Hsieh *et al.*[6]. Substituted ortho-(trimethylsilyl)phenyl triflate was reacted with different isocyanates in CsF as base in CH_3CN at 70 °C which produced corresponding substituted diphenylamine (Scheme I.5). This protocol tolerates various functional groups on both sides.

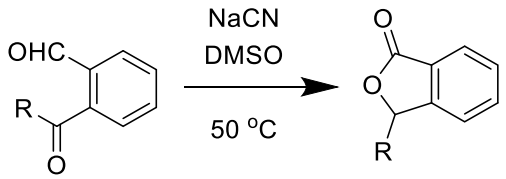


Scheme I.5. Coupling reaction of isocyanates 116 and benzynes by CsF.

I.A.2. C-O bond formation reaction

Bond formation between C-O bear huge importance in organic chemistry and vast list of publications are present on this specific topic. Large array of produccs can be synthesized following this bond formation between C-O like ethers, epoxides, lactols, carboxylic acids, lactones, carbonate derivatives, imino ethers, thiocarbamates, hemiacetals, esters, isoureas, thionoesters, nitrites and many more.

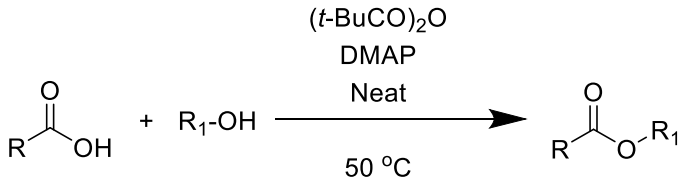
H.G. Schmalz *et al.* reported recently facile conversion of 2-formyl-arylketones into 3-substituted phthalides in presence of NaCN in DMSO at 50 °C[7]. This reqction is explored in a Cannizarro-Tishchenko-type reaction under nucleophile catalysis (NaCN) or under photochemical conditions (Scheme I.6).



Scheme I.6. Synthesis of 3-substituted phthalides in NaCN and DMSO.

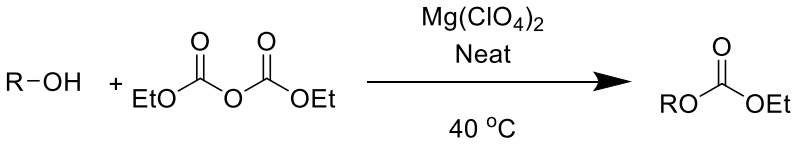
K. Ishihara *et al.* explored esterification by only a 0.05−2 mol % of DMAP with alcohol and carboxylic acids[8] of various types to produce good yield of products (Scheme I.7). The process

has been done under auxiliary base- and solvent-free conditions to give the corresponding esters. Further they have recycled the polystyrene supported DMAP several times and reused.



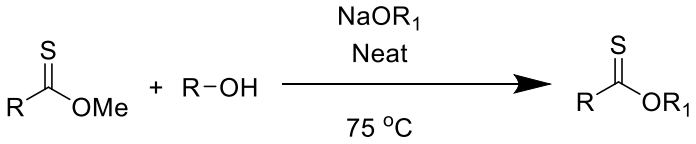
Scheme I. 7. Synthesis of ester in DMAP in neat condition.

Aryl or alkyl carbonates are another important group formed by C-O bond formation reactions. L. Sambri *et al.* reported an easy conversion of alcohol to aryl and alkyl carbonates[9] by using $Mg(ClO_4)_2$ in solvent-free condition in presence of 1,3-dicarbonyl compound (Scheme I.8). Versatile products have been achieved by this reaction process in good yield.



Scheme I.8. Synthesis of aryl and alkyl ethyl carbonates by $Mg(ClO_4)_2$ in solvent-free condition.

A recent advancement of thionoesters in very good yields is reported by C.M. Friesen *et al.* in alcohol as solvent in various sodium alkoxides[10]. This process produces excellent yield while methanol by product is simultaneously separated from the reaction mixture (Scheme I.9). Benzyl and alkyl thionobenzoates and thionoheterobenzoates were competently prepared using numerous alcohols.

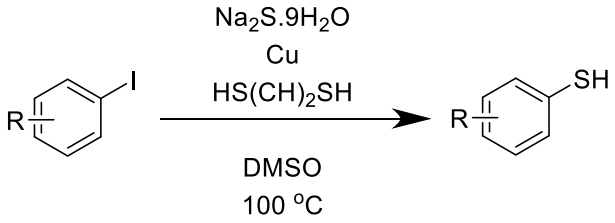


Scheme I.9. Transesterification of Thionoesters in presence of sodium alkoxide in neat condition.

I.A.3. C-S bond formation reaction

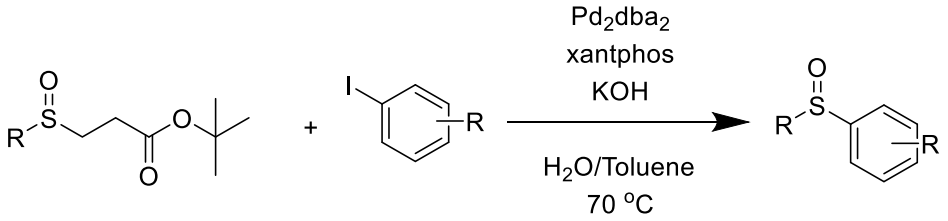
Vast array of compounds which has huge importance in organic chemistry bear C-S bond in their structures such as, thiophenols, thioesters, sulfides, sulfoxides, sulfones, sulfonic acids, sulfonamides, sulfanamides, thiosulfonates, isothioureas, thiocyanates etc. Therefore, for synthesis of those important compounds thorough study of C-S bond formation reactions are purely of interest.

Y. Liu *et al.* reported conversion of iodoarenes into thiophenol by easily available Na_2S, 1,2-Ethanedithiol in DMSO at 100 ^oC[11]. Copper is used as catalyst in this process and any iodine derivative can produce very good yield in this process (Scheme I.10).



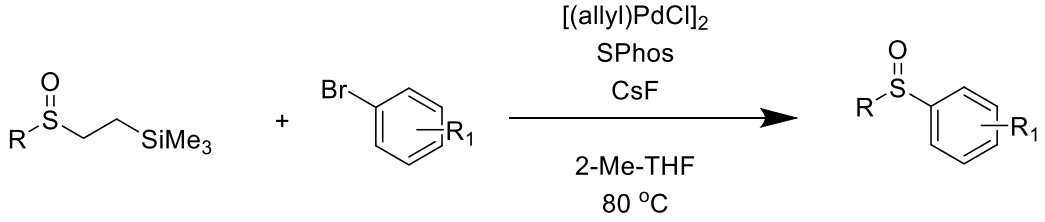
Scheme I.10. Synthesis of thioamides by Cu as catalyst in DMSO.

Another important compound is aryl sulphoxide investigated by G. Poli *et al.* Paladium is used as catalyst in this case and arylation of sulfenate anions produced from β-sulfinyl esters is generated under basic biphasic conditions in this reaction[12]. This reaction gives a simple, mild, efficient route to aryl sulfoxides in excellent yields (Scheme I.11).



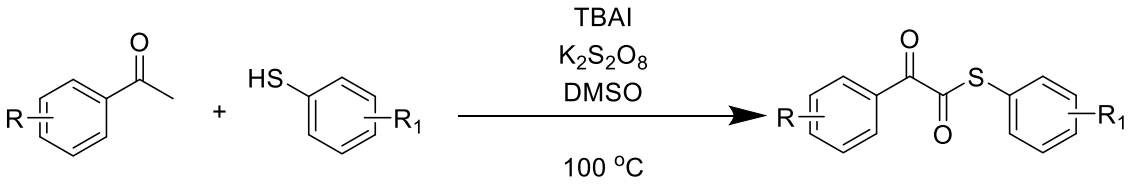
Scheme I.11. Synthesis of aryl sulfoxides catalyzed by Pd.

P.J. Walsh *et al.* reported mild preparation of aryl sulfones in Pd catalyzed condition using alkyl 2-(trimethylsilyl)ethyl sulfoxides in CsF and 2-Me-THF at 80 ^oC[13]. The success of this process lies within the use of mild reaction condition sue to base sensitivity of the reactants, intermediated and products its often difficult to achieve good yield. This protocol however furnishes high yield with various derivatives of the reactants (Scheme I.12).



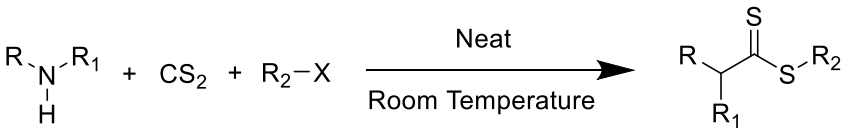
Scheme I.12. Synthesis of sulphones in Pd catalyzed THF medium.

In recent development of C-S bond formation F. Yu *et al.* reported metal-free thioester formation from methyl ketones in presence of TBAI[14]. DMSO is used as solvent in this protocol and the reaction is done at 100 ^oC. This reaction offers large scale production option for thioesters and it has broad functional group tolerance (Scheme I.13).



Scheme I..13. Synthesis of α-ketothioesters in metal-free condition.

Added, in metal-free approach for C-S bond formation M. R. Saidi *et al.* reported a mild and efficient method for synthesis of dithiocarbamates in neat condition at room temperature[15] by amines, carbon disulphide and aryl and alkyl halides with high yield of products. Catalyst-free process at room temperature and without using any solvent makes this process green and sustainable too (Scheme I.14).

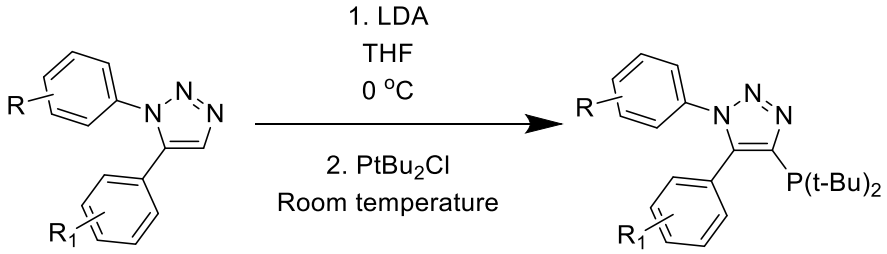


Scheme I.14. Synthesis of dithiocarbamates in solvent-free condition at room temperature.

I.A.4. C-P bond formation reaction

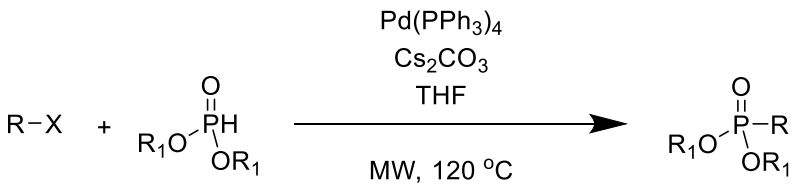
Various compounds with C-P hetero bond also have utmost importance in organic chemistry like phosphines, phosphine oxides, phosphonates, thiophosphines, phosphinates and its acid derivatives, thiophosphonates and its derivatives etc.

Monophosphine ligands are an important class of ligands and X. Zhang *et al.* proposed preparation of triazole based monophosphine ligands via cycloaddition[16]. These ligands complexing with Pd provides a very efficient catalyst for Suzuki-Miyaura coupling and also applicable in amination reactions of aryl chlorides (Scheme I.15).



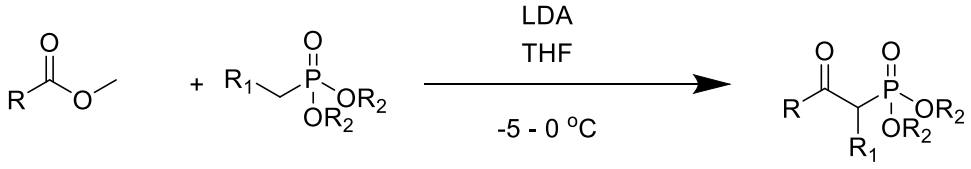
Scheme I.15. Synthesis of Triazole-based monophosphine ligands by cycloaddition.

J. Stawinski *et al.* reported production of phosphonates using palladium catalyst, $Pd(PPh_3)_4$[17]. They reported a cross coupling reaction between aryl and vinyl halides at 120 °C under microwave irradiation with various H-phosphonate diesters (Scheme I.16). The reaction occurs within 10 minutes with retention in configuration.



Scheme I.16. Synthesis of phosphonates by Pd catalyzed reaction under MW irradiation.

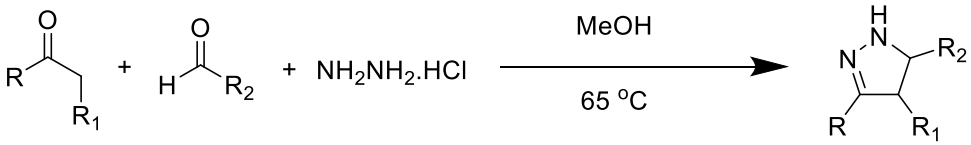
Another advancement of C-P bond formation reaction has been reported by J. Y. L. Chung *et al.* for synthesis of β-Ketophosphonates by condensation of esters and phosphonates[18]. The reaction is catalyzed by Lithium diisopropylamide and temperature requirement is 0 °C (Scheme I.17). This protocol provides prominent yield of the product with promise of easy operation and large scalability.



Scheme I.17. Synthesis of β-Ketophosphonates by LDA.

I.A.5. Synthesis of pyrazolines

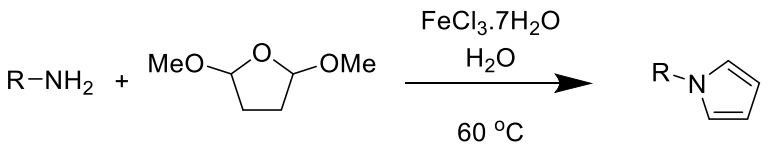
In recent years, heterocyclic motif formation by C-N bond formation have also gained lots of interest among chemists. Such a heterocycle formation is reported by R. Faessler *et al.* for the formation of substituted pyrazoles in a one -pot three component synthesis from ketones, aldehydes and hydzine monochloride[19]. This reported protocol readily produces desired pyrazoles under metal-free condition in MeOH as solvent at 65 °C. A variety of pyrazoles can be obtained with good yield by this process (Scheme I.18).



Scheme 1.18. One -pot synthesis of pyrazoles in metal-free condition in MeOH.

I.A.6. Synthesis of pyrroles

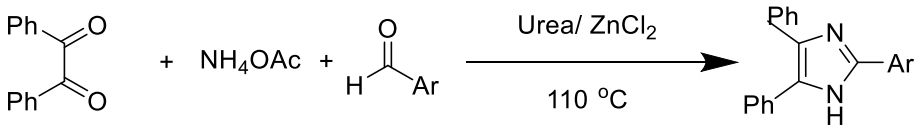
Pyrroles are generally prepared by conversional Paal-Knorr pyrrole condensation. Recently, M. R. Saidi *et al.* reported an efficient method[20] for *N*-substituted pyrrole synthesis by condensation of 2,5-dimethoxytetrahydrofuran with several amines, sulfonamines in water in the presence of a catalytic quantity of iron(III) chloride. This reaction is done in mild reaction condition at 60 °C (Scheme I.19).



Scheme I.19. *N*-substituted pyrroles in the presence of a catalytic amount of iron(III) chloride.

I.A.7. Synthesis of imidazoles

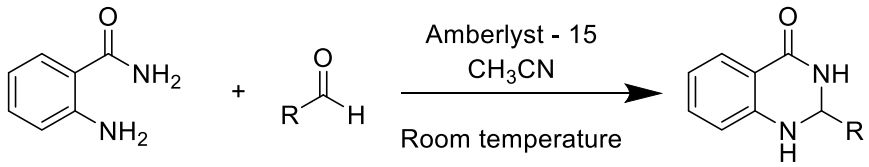
C. Ochoa-Puentes *et al.* reported an easy and efficient method for the preparation of imidazole from dicarbonyl compound along with ammonium acetate and organic aldehyde[21]. Mild reaction condition is used as only $ZnCl_2$/ Urea is employed as catalyst at 110 °C. The reaction completes within 30 minutes adds advantage to the protocol (Scheme I.20).



Scheme I.20. Synthesis of imidazoles from dicarbonyl compounds in urea/$ZnCl_2$.

I.A.8. Synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones

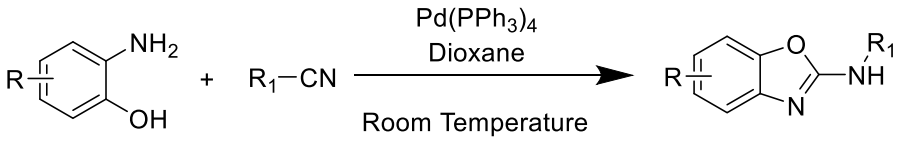
Quinazolinone is one of the most important heterocycles having C-N bond. An advancement of the study has been done by P. V. N. S. Murthy *et al.* reported green and efficient synthesis of 2,3-dihydro quinazolin-4(1*H*)-ones using Amberlyst-15 as a catalyst at room temperature[22]. A number of dihydro quinazolinone derivatives have been synthesized successfully from aldehyde and 2-aminobenzamide. Acetonitrile has been used as solvent in this reaction (Scheme I.21).



Scheme I.21. Synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones catalyzed by Amberlyst-15.

I.A.9. Synthesis of 2-aminobenzoxazoles

2-aminobenzoxazoles exhibit C-N as well as C-O bond formation reaction. B. Liu *et al.* reported efficient method of preparation of palladium catalyzed 2-aminobenzoxazoles. Isocyanides with *o*-amino phenols in aerobic condition at room temperature[23]. The scope of this reaction is also explored by them for synthesis of other *N*-hetero systems (Scheme I.22).



Scheme I.22. Synthesis of 2-aminobenzoxazoles catalyzed by palladium.

I.B. Conclusion

In this chapter we have observed immense importance of carbon- hetero bond formation reaction in present day chemical, biological and pharmaceutical advancements. Moreover, any bioactive natural product also has C-hetero bond present in its structure. We have also observed cyclisation of various precursors into heterocyclic compounds to yield important parts of bioactive motif. The scope in this topic is definitely huge and we have tried to explore the same. In many cases we have observed use of toxic metals, costly catalysts, hazardous reaction conditions for synthesis of C-hetero bonds. Further solvents also play an important role in making the protocol hazardous and economically unfavourable. Therefore, we felt necessary to step towards greener, cost effective, environmentally sustainable catalyst and solvent mediated formation of C-hetero bonds in a straightforward approach.

I.C. References

References are given in BIBLIOGRAPHY under Chapter I.